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The normal distribution of the hypoxic ventilatory response and methodological impacts: a meta-analysis and computational investigation

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Abstract

The hypoxic ventilatory response (HVR) is the increase in breathing in response to reduced arterial oxygen pressure. Over several decades, studies have revealed substantial population-level differences in the magnitude of the HVR as well as significant inter-individual variation. In particular, low HVRs occur frequently in Andean high-altitude native populations. However, our group conducted hundreds of HVR measures over several years and commonly observed low responses in sea-level populations as well. As a result, we aimed to determine the normal HVR distribution, whether low responses were common, and to what extent variation in study protocols influence these findings. We conducted a comprehensive search of the literature and examined the distributions of HVR values across 78 studies that utilized step-down/steady-state or progressive hypoxia methods in untreated, healthy human subjects. Of these studies, 35 (59.3%) were moderately positively skewed (skew>0.5), and 21 (35.6%) were significantly positively skewed (skew>1), indicating that lower HVR values are common. The skewness of HVR distributions does not appear to be an artifact of methodology or the unit with which the HVR is reported. Further analysis demonstrated that the use of step-down hypoxia versus progressive hypoxia

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AUTHOR CONTRIBUTIONS

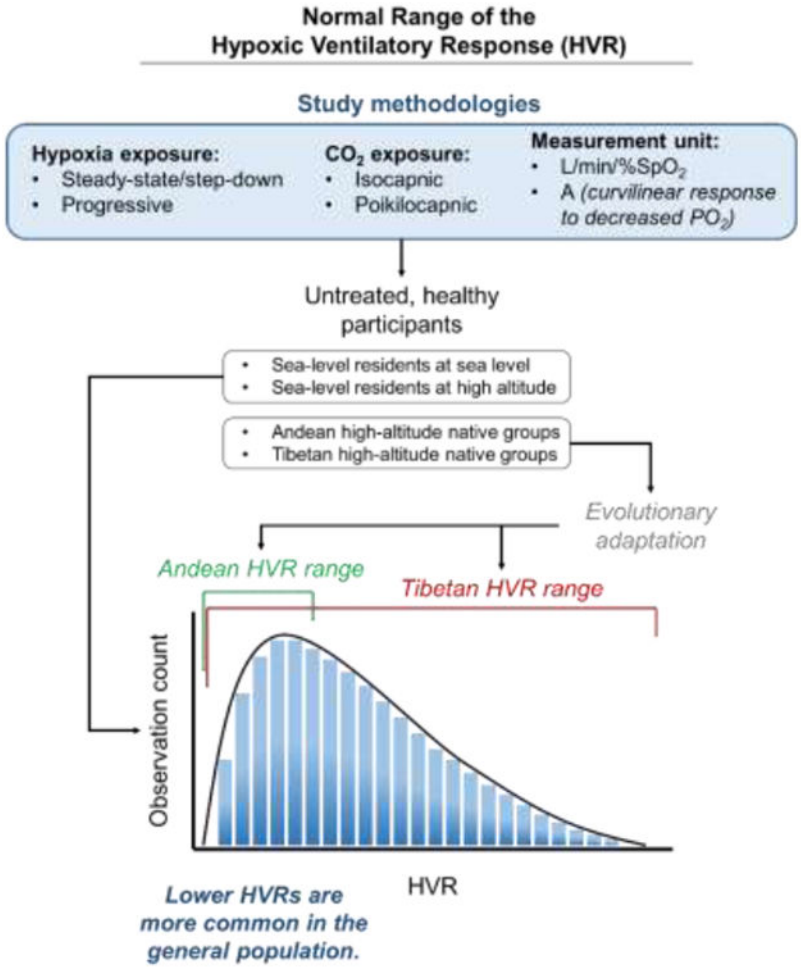
ECH, FP, BO, and KP conceived and designed the research. BO, KP, and ECH collected data, interpreted the data analysis, and prepared figures. MO, DJD, and EG provided unpublished HVR data used in the study. BO, KP, and ECH drafted the manuscript. BO, KP, ECH, and FP revised the manuscript. BO, KP, ECH, FP, MO, DJD, and EG approved of the final version of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

methods did not have a significant impact on average HVR values, but that isocapnic protocols produced higher HVRs than poikilocapnic protocols. This work provides a reference for expected HVR values and illustrates substantial inter-individual variation in this key reflex. Finally, the prevalence of low HVRs in the general population provides insight into our understanding of blunted HVRs in high-altitude adapted groups.

Graphical Abstract



In this meta-analysis, we examine hypoxic ventilatory response (HVR) distributions across 78 studies in which healthy, untreated participants from diverse populations were examined under several testing conditions (i.e., step-down or progressive hypoxia, and isocapnic or poikilocapnic CO_2 methods) and units of measurements (i.e., L/min/SpO_2, A unit). We find that lower HVR values are more common amongst the general population and that higher HVR values are uncommon. We also impacts of methodology on HVR measurements, including higher HVRs observed in isocapnic protocols, but no significant impact of step-down versus progressive hypoxia methods. These results provide key insight into understanding the evolutionary adaptation of the HVR in high-altitude native populations, as well as comparative interpretations of HVR measurements across studies.

Keywords

hypoxic ventilatory response; HVR; hypoxia; ventilation; variation; population variation

INTRODUCTION

The hypoxic ventilatory response (HVR) is the increase in breathing in response to reductions in arterial oxygen partial pressure (Pa_{O2}). This reflex is the body's first defense against oxygen limitation. During an acute hypoxic stimulus (seconds to minutes), changes in arterial P_{O2} are detected by the peripheral (carotid body) chemoreceptors. This leads to increased afferent input to the respiratory centers and reflex activation of respiratory muscles which increase tidal volume (V_T) and frequency (f_R) of breathing (Pamenter & Powell, 2016). The amplitude of this response is dependent on the arterial P_{CO2} (Pa_{CO2}), with larger increases in total ventilation occurring for the same drop in Pa_{O2} when Pa_{CO2} is higher.

There is significant individual variation in HVR sensitivity which may drive susceptibility to, or protection against, hypoxia-related pathologies. In the context of high-altitude physiology and medicine, studies have linked HVR to exercise performance at altitude (Schoene et al., 1984; Masuyama et al., 1986), susceptibility to high altitude pulmonary edema (HAPE) (Hackett et al., 1988; Matsuzawa et al., 1989), and development of acute mountain sickness (AMS) (Moore et al., 1986b). In clinical cases, high respiratory drive in response to hypoxemia may result in patient self-inflicted lung injury in acute respiratory distress syndrome (ARDS) (Vassilakopoulos et al., 2004; Wang et al., 2005; Spinelli et al., 2020), and high or low hypoxic ventilatory responses may exacerbate central and obstructive sleep apnea syndromes, respectively (Solin et al., 2000; Ainslie et al., 2013). Finally, low HVRs may have contributed to "silent hypoxemia" in COVID-19, in which patients presented with very low arterial oxygen levels but minimal dyspnea (Nouri-Vaskeh et al., 2020; Tobin et al., 2020; Bickler et al., 2021; Swenson et al., 2021).

Given the critical role of the HVR in determining the physiological consequences of hypoxic episodes, it is important to understand the natural variation in this reflex, how it differs across populations, and how this trait can be used to predict susceptibility to hypoxia-promoted diseases. Furthermore, understanding the normal distribution of this trait among the general population will provide valuable information to guide clinical decisions. This will also inform our understanding of possible genetic determinants of the HVR. Previous work has demonstrated that this ventilatory reflex is low, or "blunted", in high-altitude Andean native populations compared to other high-altitude native groups, as well as sea-level residents. This blunted HVR has been described as a unique adaptation, or maladaptation, to the high-altitude environment. However, it is possible that this phenotype is also common in lowlanders, and that these individuals may share genetic variants associated with lower HVR. Therefore, the goal of this meta-analysis is to quantitatively examine the available literature on the HVR to determine the normal distribution of this reflex and how methodology impacts the measured ventilatory sensitivity to hypoxia. Throughout several years of collecting HVR measurements in diverse populations, we observed that high HVRs appear to be uncommon in healthy sea-level populations. We

therefore aimed to test the hypothesis that low HVR values are more common in the general population and that this result is not dependent on the specific method used. To test this hypothesis, we collected and analyzed HVR values, methodological details, and population demographics from all published studies examining the HVR which include raw data.

METHODS

Literature summary and data extraction

We conducted a literature search following the PRISMA guidelines for systematic reviews and meta-analyses to identify peer-reviewed studies reporting individual HVR measurements in healthy populations (Page et al., 2021). The search was conducted on August 12, 2021. Papers were located via PubMed searches for “hypoxic ventilatory response” or “hypoxic chemosensitivity” across any time period. Studies were then screened for titles which indicated that HVR measurements were made or that respiratory reflexes or chemoreflexes were measured in humans, and that the paper was not a review. Studies were then screened for abstracts that indicated the appropriate HVR measures were made and included at least one group of healthy subjects receiving no additional experimental intervention. Finally, a complete review of each remaining paper for methodological details was conducted. Published studies that included mean or raw individual HVR data in table or scatterplot form, as well as sufficient participant demographics and methodological information to determine the type of HVR test conducted, were included in our analyses. At each step of the filtering process, titles, abstracts, or whole studies were evaluated by two reviewers and disagreements were settled by a third reviewer.

Raw data was extracted from eligible studies. Individual HVR measures for each participant had to be provided in a table, as a scatterplot with individual points, or in supplementary data. For scatterplot data, values were extracted from graphs with the Image Calibration tool in ImageJ (National Institutes of Health, MD, USA). In one study, hundreds of HVR measures were provided in scatterplot form. This may have led to the exclusion of some individual data points from this study due to overplotting. Studies reporting measurements in distinct populations (i.e., high-altitude versus sea-level populations) were separated into subgroups by population to ensure that across-population differences in HVR characteristics were accounted for.

Methodological details for each study were collected as categorical variables. Eligible studies were classified as using step-down/steady-state or progressive hypoxia administration methods. Step-down or steady-state HVR tests involve measuring total ventilation after several minutes of equilibration to two or more constant fractions of inspired oxygen (F_IO_2), arterial oxygen pressures (P_aO_2), or arterial oxygen saturation (SpO_2) targets and calculating the change in ventilation across two O_2 levels. Progressive tests involve rebreathing or other methods which produce a continuous decrease in inspired PO_2 over time. In this case, the HVR is calculated as the curvilinear relationship between total ventilation and PO_2 (Weil et al., 1970). CO_2 status during the protocol was classified as “isocapnic” if end-tidal PCO_2 was maintained at a constant level while O_2 was manipulated, or “poikilocapnic” if end-tidal PCO_2 was allowed to decrease freely with hyperventilation. The elevation at which measurements were made was also recorded. When the altitude

of measurement was not provided, it was determined from the location of measurements (if provided). If neither elevation or exact location of measurements were provided, the measurement elevation was assumed to be the elevation of the corresponding author's home institution or institution providing IRB approval. Age was included in the dataset only if individual ages were provided for each participant. Participants were assumed to be of sea-level ancestry if data was collected at sea level and there was no other indication of participant ancestry. Units of measurement (A or L/min/%SpO_2) and target hypoxic values were also recorded (as SpO_2, F_IO_2, P_IO_2, P_AO_2, or P_aO_2).

Collected measurements were limited to cases in which HVR measurements were made under resting conditions at any altitude. Measurements made under additional experimental conditions (e.g., exercise, hypercapnia, head-down tilt angles, sleep) were not included. However, if a study utilizing these treatments also included baseline measures under no treatment condition, these baseline measures were included. In one case, measurements taken with a head up tilt of 85° were utilized (Hildebrandt et al., 2000a) since this angle is often utilized in seated participants during HVR measures. If several HVR measures were conducted in short succession (Basaran et al., 2016), only the first measure was included in our dataset, when provided, to allow comparison across studies and prevent the inclusion of HVR values elevated by prior intermittent hypoxia exposure. Of note, several studies conducted HVR measures in duplicate or triplicate and reported means.

For studies targeting a specific inspired oxygen pressure or fraction, an estimated corresponding saturation value was determined to facilitate comparisons of hypoxia targets across studies. These calculations were based on the Severinghaus equations for human blood O_2 dissociation computations at a pH of 7.4 and temperature of 37°C (Severinghaus, 1979). Arterial PO_2 was estimated from inspired PO_2 using the alveolar gas equation with the A-a gradient calculated as (age + 10) / 4 (Sharma et al., 2019; Hantzidiamantis & Amaro, 2022). An alveolar-arterial oxygen gradient of 10 was used if participant age was not provided. This value was determined by calculating the normal A-a gradient for a healthy individual aged 33 years, since this was the average age of all participants in the total dataset.

Comparison with within-lab controlled datasets

In a separate analysis, we gathered HVR values collected in a single laboratory using the same methodology to determine how mean and skew values compared to the larger literature. Each of these studies used isocapnic, step-down hypoxia protocols. 7 datasets were included in this separate analysis, 4 of which are published and 3 unpublished. Of the four published studies, three were included in the larger literature review (Garcia et al., 2000b; Hupperets et al., 2004; Basaran et al., 2016) and one was excluded due to the inclusion of intravenous infusions during testing (Weinger et al., 1998). Three additional unpublished datasets were included which utilized the same protocol. For each dataset, only HVR measures collected at sea level under no treatment condition were included.

Data simulation

Data recovered in the meta-analysis included data reported in two unit types: “A” or “L/min/SpO_2”. The unit A is the mathematical parameter which determines the curvilinear shape of the ventilatory response to changes in PO2, with higher A values representing higher HVRs. Alternatively, the L/min/SpO_2 unit represents the linear change in ventilation as a function of SpO_2 or SaO_2. Since a primary goal of this study is to determine the distributions of HVR values across populations and methodologies, we aimed to determine if HVRs reported in different units were comparably distributed, or if the use of the L/min/SpO_2 unit preferentially produced the skewed distributions we observed.

Similarly, it was unclear if the degree of hypoxia administered during the test impacted the skewness of the data. In particular, we hypothesized that higher positive skewness would be observed for the same dataset if values were reported in L/min/SpO_2 and utilized a modest SpO_2 target. However, since no dataset included both A values and L/min/SpO_2 values within the same individuals, we prepared a simulated dataset to address this question.

We first simulated a set of 500 random HVR curves, and their corresponding A and V_E^0 values, constrained by the mean and standard deviation of HVR values reported in Weil et al. (1970) (means: A = 180.2 ± 14.5; V_E^0 = 4.8 ± 0.3). For each curve, four P_AO_2 values were chosen (120, 50, 40, 37 mmHg) to represent normoxic as well as mild, moderate, and severe hypoxic targets respectively, based on commonly used HVR protocols. Ventilation values corresponding to each P_AO_2 value were then calculated for each curve based on the following equation:

$$V_E = V_{E0} + \frac{A}{P_{AO2} - 32}$$

To convert these simulated HVR values from A to L/min/%SpO_2 units, we first calculated arterial oxygen saturations at the four chosen P_AO_2 values directly from the standard oxygen dissociation curve using an A-a gradient of 10 as described above. These calculations were conducted using the Kelman strategy which allows the calculation of SO_2 or PO_2 at various temperatures, carbon dioxide levels, and pH levels based on data from Severinghaus (1966) (Kelman 1966). As such, P_AO_2 values of 100, 70, 55, and 48 mmHg correspond to arterial saturations of 96.8, 91.0, 80.4, and 71.1%, respectively, assuming a PCO2 of 40, pH of 7.4, and temperature of 37°C.

HVR values were determined for each of the 500 ventilatory response curves based on the calculated increase in ventilation from baseline (P_AO_2 = 120 mmHg) to each hypoxic target (P_AO_2 = 50, 40, and 37 mmHg) as

$$HVR = \frac{\Delta V_E}{\Delta SaO_2}$$

Statistical analysis

All statistical analyses and data simulations were conducted in R Studio (Version 1.4.1717). Summary statistics were calculated in R using the *psych* package. To determine if data were

normally distributed or skewed, Kolmogorov-Smirnov statistics are provided for datasets of $N \geq 50$, and Shapiro-Wilks statistics are provided for datasets of $N < 50$. Comparisons of HVR values across methods were conducted with unpaired t-tests after removal of extreme outliers (see results). Additional general linear models were used to determine if significant relationships were upheld after adjusting for cofactors such as PO_2 or PCO_2 method, sex, and study population. To test for significant differences in mean HVR values across studies with the lab-controlled dataset, one-way ANOVAs and post-hoc Tukey HSD tests were used. For correlation analyses, Shapiro-Wilk normality tests were first conducted, and Spearman rank correlations were utilized for non-normally distributed datasets. Data are reported throughout the paper as means ± standard deviation and error bars represent 95% confidence intervals.

RESULTS

Study filtering

The initial literature search revealed 861 records. Of these, 630 were removed during title filtering and 71 were removed during abstract filtering. A final subset of 160 studies received complete review. After this review, 78 studies remained in the final dataset and provided either mean or raw HVR values and sufficient methodological detail to include in this analysis (Figure 1) (Doekel et al., 1976; Zwillich et al., 1977; Riley et al., 1977; Scoggin et al., 1978; Hackett et al., 1980, 1988; Stanley et al., 1983; White et al., 1983, 1987*b*; Ward, 1984; Moore et al., 1984, 1986b, 1986a; Tanaka et al., 1986; Aitken et al., 1986; Okita et al., 1987; Regensteiner et al., 1988, 1989, 1990; Milledge et al., 1988, 1991; Matsuzawa et al., 1989; Levine et al., 1992; Gold et al., 1993; Selland et al., 1993; Zhuang et al., 1993; Reeves et al., 1993; Chowdhury et al., 1993; Amin et al., 1994; Kikuchi et al., 1994; Feiner et al., 1995; Swenson et al., 1995; Harms & Stager, 1995; Markov et al., 1996; Sato et al., 1996; Redline et al., 1997; Beall et al., 1997; Katayama et al., 1999, 2000, 2001, 2002; Garcia et al., 2000a, 2000*c*; Hildebrandt et al., 2000b; Warren et al., 2000; Prisk et al., 2000; Zhang & Robbins, 2000; Jokic et al., 2000; Muza et al., 2001; Teppema et al., 2002, 2005, 2006; Bärtsch et al., 2002; Pokorski & Marczak, 2003b, 2003a; Bhaumik et al., 2003; Drumm et al., 2004; Hupperets et al., 2004; Koehle et al., 2005; Spicuzza et al., 2005; Teichtahl et al., 2005; Terblanche et al., 2005; Brutsaert et al., 2005; Karan et al., 2005; Foster et al., 2005; Lusina et al., 2006; Steinback & Poulin, 2007; Faulhaber et al., 2012; Kovtun & Voevoda, 2013; Albert & Swenson, 2014; Caravita et al., 2015; Basaran et al., 2016; Pfoh et al., 2016, 2017; Goldberg et al., 2017; Smith et al., 2017; Broens et al., 2019). The complete dataset with additional details including study populations and location of measurements is located in Table S1. Several individual studies included multiple datasets which we evaluated separately due to differences in methodology, treatment (such as measures made at sea level versus high altitude), or study population. This yielded 132 separate data sets for analysis. Of these 132 datasets, 31 reported HVR units as A values (23.5%) and 101 reported L/min/SpO_2 units (76.5%). 119 datasets utilized isocapnic protocols (90.2%) and 13 used poikilocapnic protocols (9.8%). 93 used progressive hypoxia or rebreathing methods (70.5%) and 39 used step-down or step-down methods (29.5%).

Summary of HVR measurements across all studies reporting raw data

In the final analysis, 72 datasets reported mean HVR values and 60 datasets provided raw HVR datasets. Across all studies, the mean HVR was 126.0 ± 69.2 for reported A units, and 0.98 ± 0.89 for reported L/min/SpO_2units. Density plots demonstrating the distribution of measurements in each study that included raw HVR values are provided in Figure 2. We calculated the skewness of HVR distributions for each of these datasets. Of the 60 datasets reporting raw HVR values, 35 (58.3%) were at least moderately positively skewed (skew>0.5), and 21 (35%) were significantly positively skewed (skew>1). Notably, no studies showed moderate or significant negative skew. Therefore, HVR distributions tend to be at least moderately positively skewed in nearly half of all studies, indicating that lower HVR values are more common. Skewness for all studies that included raw HVR measurements was determined via Shapiro-Wilks tests for normality. 24 out of 72 datasets (33.3%) were significantly different from a normal distribution (Table S2).

Impact of methodology on the HVR and its distribution

Since reported HVR values display significant positive skewness, we aimed to determine if specific HVR methodologies contributed to this result, or to the mean HVR value. For this analysis, we included additional tests with only studies conducted at sea-level since HVR increases with high-altitude acclimatization and differs across native high-altitude populations. The initial analysis revealed two extreme within-study outliers, in study 6 and 24, who were reported to have HVR values of 11 and 7.5 L/min/SpO_2, respectively (Figure S1a). These outliers were removed in the subsequent analyses. Additionally, datasets 55b-k were removed due to extreme outlier means within these high-altitude acclimatized group of datasets (Figure S1b). These studies are later examined independently to explore the impact of high-altitude acclimatization on the HVR.

After removing outliers, the mean HVR across all populations was 126.0 ± 69.2 for studies reporting A units, and 0.70 ± 0.38 L/min/SpO_2. For studies conducted in sea-level residents at sea-level, the mean HVR was 121.0 ± 56.6 for studies reporting A units and 0.65 ± 0.34 L/min/SpO_2. Within studies reporting HVR in L/min/SpO_2 units, both step-down and progressive methods were used to manipulate inspired oxygen. There was no significant impact of progressive versus step-down methods on average HVR across all studies ($t(53.9) = 0.72$, $p=0.469$, Figure 3A), or within sea-level studies only ($t(44.0)=-0.49$, $p=0.626$, Figure 3D). HVRs were higher on average when measured with isocapnic protocols (all studies: $t(13.4)=3.4$, $p=0.004$, Figure 3B; SL only: $t(11.4)=3.0$, $p=0.01$, Figure 3E). This relationship was also observed in studies reporting A units (all studies: $t(28.6)=4.9$, $p<0.001$, Figure 3C; SL only: $t(24.5)=5.3$, $p<0.001$, Figure 3F), however only 2 datasets included A units with poikilocapnic methods. The significant effect of CO_2 method on HVR remained after adjusting for O_2 method and study population in studies reporting HVR in L/min/SpO_2 units ($p=0.002$). This relationship was not upheld in studies reporting A values ($p=0.188$), although there were only 2 datasets in this group utilizing poikilocapnic methods, so we are underpowered to make this comparison in this group. Furthermore, among step-down methods using isocapnic protocols, there was a significant positive association between the end-tidal PCO_2 target and the mean HVR across studies via a Spearman rank correlation analysis ($rho = 0.55$, $p=0.017$) (Figure 4).

Across all studies, the unit used to report HVR did not significantly impact the skew of the data distribution (A: skew = 0.86 ± 0.59, L/min/SpO_2: skew=0.71 ± 0.66, t(13.8)=0.68, p=0.507, Figure 5A). This remained true after adjusting for methodologies and population in linear models (p=0.741). There was also no impact of step-down versus progressive (t(27.2)=1.3, p=0.208) or isocapnic versus poikilocapnic methods (t(13.4)=−2.1, p=0.059) on skewness (Figure 5B–C), although there was a nonsignificant trend for higher skewness in studies using progressive hypoxia administration and poikilocapnia. Interestingly, linear models examining the impact of unit, methodology, and population on skewness indicated a significant, but modest, impact of CO_2 method on skew in studies reporting HVR in L/min/SpO_2 units (p=0.007, adj. model R^2=0.10), but no impact of CO_2 method in studies reporting A units (p=0.575).

Studies used a wide range of hypoxia targets (Figure 6). The mean SpO_2 hypoxia target was 77.2 ± 7.2%. Since step-down methods allow the participant to stabilize at the hypoxia target for a longer period of time, the targets for studies using this method were typically higher (85.4 ± 6.9%). The mean end-tidal PO_2 hypoxia target was 41.7 ± 3.4 mmHg for all studies and 46.9 ± 2.4 mmHg for step-down methods. The mean F_IO_2 hypoxia target was 9.4 ± 3.4% for all studies, and 10.8 ± 2.5% for step-down methods. Two studies utilized quite low SpO_2 hypoxia targets of 55% and 45% (Hackett et al., 1988; Gold et al., 1993). The study utilizing a 45% target applied a rebreathing technique and this was the threshold at which the test was terminated unless the participant became distressed. The study using a 55% target replicated the Rebuck and Campbell rebreathing technique (1974). Therefore, both studies with the lowest hypoxia targets would not have maintained these low SpO_2 levels for prolonged periods as is typically done with step-down methods.

To determine if the hypoxia target had a significant impact on HVR, we first conducted Spearman rank correlations on mean HVR values collected at sea-level as a function of author-reported SpO_2, end-tidal PCO_2, and F_IO_2 hypoxia targets. In the overall dataset, for studies reporting HVR in L/min/SpO_2 units, there was no relationship between reported SpO_2 or end-tidal PO_2 hypoxia target and mean HVR across studies (SpO_2: p=0.99, rho=−0.002; $ETPO_2$: p=0.99, rho=0.003; Figure 7A–B). This remained true after adjusting for study source, sex, and O_2 and CO_2 methods (Adj. model R^2 = 0.35, p=0.445). A trend emerged for higher HVR values at lower F_IO_2 targets (F_IO_2: p=0.05, rho=−0.71; Figure 7C), however this also did not remain after adjusting for study source, sex, and O_2 and CO_2 methods in linear models (Adj. model R^2=−0.46, p=0.733). For studies reporting A units, multiple hypoxia targets were provided only for studies reporting SpO_2 units and there was no significant relationship (p=0.23, rho=0.32; Figure 7D). We then calculated the estimated SpO_2 level for each study using the reported end-tidal PO_2 or inspired PO_2 hypoxia target levels. With this expanded dataset, there was still no significant relationship between SpO_2 hypoxia target and mean HVR (p=0.51), and this result remained after splitting groups into isocapnic and poikilocapnic methods (isocapnic: p=0.38, poikilocapnic: p=0.69). Notably, when investigating these relationships using all available individual HVR values collected at sea-level (N=2303), there were significant increases in HVR at lower target SpO_2 and F_IO_2 targets (SpO_2: R = −0.23, p<0.001; F_IO_2: R=−0.50, p<0.001). This relationship remained for studies reporting F_IO_2 targets, but not for studies reporting SpO_2 after adjusting for study source, sex, and O_2 and CO_2 methods in linear models.

Comparison with within-lab controlled datasets

The mean and distribution of HVR values collected over 7 studies completed in the same laboratory are provided in Figure 8. Within this group, there were some significant differences across datasets ($F(6, 9.8 = 5.3, p<0.001)$). Dataset B had significantly higher mean HVR than dataset A and D (adj. $p<0.05$ for all). Dataset C had significantly higher mean HVR values than dataset A, D, and E (adj. $p<0.05$ for all). This difference across studies seems to be explained by the chosen isocapnic P_{CO2} targets. Of the published studies, dataset B utilized an isocapnic target 3.8 mmHg above the eupneic PCO_2 level and dataset C utilized an isocapnic target of 4 mmHg above the normoxic baseline PCO_2. In contrast, studies A and D maintained isocapnia at the eupneic level, resulting in a comparatively lower HVR value. Overall, there was no significant difference in the mean HVR measured across this dataset and the dataset from our literature review ($t(6.6) = -0.76$, $p=0.47$). There was also no significant difference in skewness ($t(7.1) = 1.0$, $p=0.34$) and overall these datasets demonstrated a mean positive skew of 0.35.

Impact of the duration of high-altitude acclimatization on HVR

21 datasets across 7 studies reported HVR values at high altitude over various periods of acclimatization ranging from 1 to 56 days (Muza et al., 2001.; White et al., 1983, 1987; Hackett et al., 1988; Bärtsch et al., 2002; Hupperets et al., 2004; Basaran et al., 2016; Smith et al., 2017). Only one dataset reported A values and was therefore excluded (Muza et al., 2001). Another dataset did not specify the exact time period of acclimatization and was also excluded (Hackett et al., 1988). This left 19 datasets across 6 studies. Among the remaining datasets, the altitude of measurements ranged only from 3800 to 4559 m elevation. Across this relatively narrow elevation range, there was a significant increase in HVR measured across studies as a function of time spent at high altitude ($p<0.001$, $Rho=0.7$) (Figure 9A). Since only one study had reported HVR values after more than 7 days of acclimatization and this study tended to report higher overall HVR values, we investigated if this relationship held after removing these datapoints at greater than 7 days of acclimatization. While a positive relationship between HVR and time of acclimatization remained in this data subset, it was no longer significant, likely due to limited datasets for analysis and across-study variability ($p=0.344$) (Figure 9B). Finally, the predicted increase in HVR at high altitude compared to sea-level measures was observed ($t(19.2)=6.10$, $p<0.0001$; SL: 0.66 ± 0.37 L/min/SpO_2; HA: 2.28 ± 1.17 L/min/SpO_2) (Figure 9C). There was no significant difference in the skewness of HVR values in datasets collected at high altitude versus sea level ($t(6.8)=-0.61$, $p=0.563$), although future work may be required to address this question since limited datasets were available for comparison at high altitude.

HVR values across sex

Of the 69 datasets including mean data only, 20 datasets across 14 studies included only men, 15 datasets across 5 studies included only women, and 34 datasets across 17 studies included both men and women in their participant cohorts. Of the 60 datasets across 44 studies including raw data, 38 datasets across 24 studies included men, and 10 datasets across 9 studies included women. Only 47% of datasets included individual participant sex data for raw HVR values out of a total of 2442 individual HVR measures. Within these

studies including individual participant HVR and sex data, there were 872 measures from men across 24 studies, and 439 measures from women across 9 studies. Notably, a majority of the measures in women were provided in Beall et al. (1997) who report an impressive 418 men and 420 women of high-altitude ancestry. Due to some overplotting in the figures from this paper, we were able to extract 360 of these HVR values in men and 347 of these HVR values in women. This means that a small subset of the remaining measures from other studies were from women (women: 92 measures from 8 studies, men: 512 measures from 23 studies).

To determine if significant differences in HVR were observed across men and women, we first examined data from studies reporting raw HVR values collected in sea-level residents at sea-level, using L/min/SpO_2 units. In linear models adjusted for O_2 and CO_2 method, as well as study source, there was no significant effect of sex on the HVR ($p = 0.196$, Adj $R^2 = 0.271$).

Data simulations

The experimental data from studies included in this meta-analysis demonstrated a potential trend for higher HVR values when lower F_IO_2 hypoxia targets were chosen. Therefore, we also conducted additional tests using simulated data to determine if lower hypoxia targets would be more likely to result in higher HVR values when using step-down methods. 500 complete HVR curves were simulated as described above. Figure 10A–B demonstrates a subset of 10 of these random HVR curves. We then calculated the HVR value for each individual curve at three different levels of hypoxia (PO_2 = 50, 40, and 37 mmHg). There was no impact of the chosen hypoxia target on the skewness of the HVR distribution. However, lower hypoxia targets result in higher mean HVR values and more variation in measurements (Figure 11). Notably, lower PO_2 levels gave higher mean HVR values when calculated as the linear relationship between ventilation rate and corresponding estimated SpO_2.

DISCUSSION

Summary of findings

- Across all studies, the mean HVR is 126.0 ± 69.2 A or 0.98 ± 0.89 L/min/SpO_2.
- HVR distributions are positively skewed, indicating that lower HVR values are more common.
- There is no significant impact of progressive versus step-down hypoxia methods on average HVR.
- Isocapnic methods produce higher HVR measures.
- HVR is elevated at high altitude compared to sea-level and increases as a function of time spent at high altitude.
- This analysis identified no significant differences in HVR across men and women, although women were largely underrepresented in available datasets.

The primary aim of this meta-analysis was to determine if low hypoxic ventilatory responses are common in the general population and how methodology impacts the magnitude and variation in HVR measurements. We examined 118 datasets from 78 separate studies which reported mean or raw HVR values in healthy adults using typical steady-state/step-down or progressive/rebreathing methods. We found that a majority of studies (58.3%) reported at least moderately positively skewed datasets (skewness > 0.5), with over one third (35%) being significantly positively skewed (skewness > 1). Notably, no studies were negatively skewed. Therefore, this result indicates that lower HVR values are typical and high HVR values are relatively uncommon.

The average amplitude of the HVR is further reduced, as expected, in studies using poikilocapnic methods, compared to isocapnic methods in which end-tidal CO_2 is not allowed to fall with hyperventilation, in both step-down/steady-state and progressive hypoxia methodologies (Figure 3). Moreover, methods using higher end-tidal PCO_2 targets for isocapnia produce, on average, higher HVR values (Figure 4). While isocapnic protocols may not represent the natural ventilatory response during environmental hypoxia exposures, in which hypoxia-induced increases in ventilation reduce arterial PCO_2, isocapnic protocols are essential for quantifying the independent peripheral chemoreflex sensitivity to hypoxia without constantly changing contributions from CO_2 and pH-sensitive peripheral and central chemoreceptors. Isocapnic protocols also allow comparisons of HVR values across individuals and studies.

This comprehensive retrospective analysis of published data clearly documents the general observation made by investigators in this field that there is a wide range of normal hypoxic ventilatory responses. Previously, there has been much discussion about blunted hypoxic ventilatory responses in high-altitude Andean native populations (see for example Moore, 2000; Brutsaert et al., 2005; Heinrich et al., 2020). It has been argued that this is a unique adaptation observed in this group, particularly when comparing these phenotypes to those observed in Tibetan high-altitude native groups (Beall, 2007). However, we found that low HVR values similar to those observed in Andean groups are also seen in sea-level residents using similar methodologies and that these low responses seem to be more common than previously appreciated. From an evolutionary perspective, the high prevalence of relatively low poikilocapnic HVRs among the general population is perhaps expected due to the fact that humans have evolved under conditions of fairly high oxygen availability with few scenarios in which chronic sustained hypoxia would be experienced. With the exceptions of native high-altitude groups, humans have inhabited primarily lower elevation areas with sufficient atmospheric oxygen conditions. Therefore, there is little selective pressure to drive natural selection on higher hypoxic ventilatory responses.

This meta-analysis also revealed a disparity in data available on the HVR in women compared to men. Of the studies including raw data, only about a quarter of them included women. With this available data, we did not find significant differences in HVR across sex groups. This is consistent with other studies reporting no differences in HVR across men and women (Bhaumik et al. 2003). However, other studies have demonstrated higher (Aitken et al. 1986) and lower (White et al. 1983; Goldberg et al. 2017) HVRs in women also. It is known that the impact of female horomones, particularly progesterone which is a respiratory

stimulant, on hypoxic chemosenstivity may lead to variable results and contribute to this confusion (Regensteiner et al. 1990; Schoene et al. 1981). Hence, this important question requires further study that should include women with HVRs measured in the context of the menstrual cycle phase, using rigorous measures of progesterone levels or menopausal state.

These results also provide insight into the prevalence of silent hypoxemia observed clinically, particularly throughout the COVID-19 pandemic. Based on the studies evaluated here, if an average patient's saturation falls 10 points, (e.g., from 95% to 85%), this would result in only a 2.8 L/min increase in breathing if not coupled with hypercapnia since the average poikilocapnic HVR is 0.28 L/min/SpO_2. Often, moderate hypoxic stimuli are not detected by the participant and these slight increases in total ventilation are achieved without dyspnea when not coupled with hypercapnia or changes in airflow resistance or lung compliance (Simonson et al., 2021). This is illustrated by the significantly lower HVR observed in studies utilizing poikilocapnic methods compared to isocapnic methods. Therefore, if CO_2 retention does not occur, it is unlikely that a substantial 10-point desaturation would cause significant hyperventilation or dyspnea. However, in more advanced cases, hypercapnia or prolonged hypoxemia resulting in ventilatory acclimatization would further increase total ventilation and more effectively stimulate dyspnea (Powell et al., 1998; Pamenter & Powell, 2016).

The increase in total ventilation as a function of arterial oxygen saturation has been described as, effectively, a linear function (Edelman et al., 1970; Weil et al., 1970). Based on the analyses conducted here, this does seem to apply when tests are performed with saturations between a 100-80% window. However, after this point, assuming PO_2 and SpO_2 fall along the normal hemoglobin-oxygen dissociation curve, total ventilation begins to increase at a faster rate as saturation continues to fall. This is observed in Figure 10 (A–B) by the increased slope of the ventilation versus PO_2 or SpO_2 curves at lower PO_2 and SpO_2 levels. Based on our data simulations, the degree to which ventilation deviates from this linear relationship below approximately 80% SpO_2 is variable across individuals (Figure 10 A–B). Nonetheless, it appears that HVR tests using two SpO_2 levels as targets can assume a linear relationship between ventilation and SpO_2 as long as the two chosen points are above 80% SpO_2. This is supported by pooled HVR data across studies using several different SpO_2 targets (Figure 7). We saw that the slope of the relationship between mean HVR and SpO_2 target was near zero, indicating that, in practice, lower SpO_2 targets did not yield higher average HVRs. The benefit of this generally linear relationship is that when conducting step-down HVR tests, one could choose any two SpO_2 levels across this linear line and obtain the same HVR value.

Weil et al. postulated about the cause of this linear relationship between ventilation and arterial PO_2 and SpO_2 in their influential 1970 paper "Hypoxic ventilatory drive in normal man." In this paper, they observed that the ventilation-PO_2 curve resembled the oxygen-hemoglobin dissociation curve and that both show inflections over the same PO_2 range. This seemed to indicate that only oxygen tensions that are low enough to lower hemoglobin oxygen saturation would stimulate ventilation. Total arterial oxygen content is primarily composed of oxygen bound to hemoglobin, and dissolved oxygen contributes minimally to the total arterial oxygen content (Siggaard-Andersen et al., 1990). Thus, a

hypoxic ventilatory response in which ventilation only increases when PO_2 is low enough to decrease hemoglobin oxygen saturation would represent an elegant evolutionary strategy for minimizing the metabolic demands of increased ventilation when hemoglobin remains highly saturated at PO_2 levels above 70-80 mmHg, and therefore increases in ventilation would lead to minimal improvements in total arterial oxygen content. This remains a useful concept for teaching the physiology of the HVR, although it has been impossible to test experimentally and there is no known physiological mechanism for sensing decreases in O_2-hemoglobin saturation directly.

The relationship between ventilation and PO_2 or SpO_2 becomes more variable at lower SpO_2 levels based on our computational investigation (Figures 10 A–B). However, since few studies use hypoxia targets lower than 75% SpO_2, we are unable to verify that this would occur *in vivo*. Although, among studies utilizing F_IO_2 targets, studies with lower targets did seem to present higher average HVR values (Figure 7C), providing some evidence that the chosen hypoxia targets can potentially impact HVR measurements, even when reporting HVR as a change in ventilation per unit change in SpO_2. The increased variability in the relationship between ventilation and SpO_2 at lower saturation levels may stem from increased individual variation in hemoglobin-oxygen binding affinity. In 2020, Balcerek et al. found that P_{50} ranged over 7 mmHg across 60 healthy individuals, with women presenting lower hemoglobin-oxygen binding affinities due to higher 2,3-BPG and BPGM levels (Balcerek et al., 2020). Thus, at a similar PO_2, and therefore a similar stimulus to peripheral chemoreceptors, different participants may present significantly different SpO_2 levels, thereby impacting the calculated HVR value.

Nonetheless, the lack of studies using hypoxia targets below 80% SpO_2 is reasonable given that this level of hypoxemia is not necessary to obtain a valid HVR measure experimentally. Furthermore, the accuracy of commercially available pulse oximeters decreases at lower SpO_2 levels (Severinghaus et al., 1989). However, in a clinical setting, it may be expected that exceptionally low PO_2 and SpO_2 levels are experienced by patients routinely, such as in severe obstructive sleep apnea, or in chronic or acute lung disease cases (Zysman et al., 2021). Therefore, it is possible that the high variability in HVR at lower SpO_2 levels may have clinical relevance in these cases and could affect disease progression. For example, high respiratory drive is often observed in patients with severe lung injury. The resulting intense respiratory effort can cause additional lung damage through “patient self-inflicted lung injury” (P-SILI) (Spinelli et al., 2020). On the contrary, a patient with lower respiratory drive may be protected against this but may also experience more severe hypoxemic stress.

Carotid body chemoreceptors play a key role in regulating arterial PCO_2, pH, and PO_2 by modulating ventilation rate, and therefore play a major role in the amplitude and plasticity of the HVR. Additionally, carotid body sensitivity influences many other physiological functions including sympathetic and parasympathetic activity, as well as cardiovascular, renal, endocrine, gastrointestinal, and metabolic effects. As a result, the carotid body dysfunction is implicated in the progression of sympathetic-related diseases such as obstructive sleep apnea, congestive heart failure, resistant hypertension, and metabolic diseases (Iturriaga et al. 2021). It is therefore an interesting possibility that the HVR may be used as a marker of carotid body function. HVR measurements have been used to assess

changes in carotid body O2-sensitivity in whole-animal experiments. Applying this idea to our results might suggest that low O2-sensitivity in carotid bodies is more common than high O2-sensitivity in healthy humans. However, the HVR also depends on translating arterial chemoreceptor activity into ventilation, which involves both neural transmission in the respiratory centers and neuromuscular function. It is not easy to separate these different mechanisms in human studies, at least, so we cannot conclude that high O2-sensitivity in carotid bodies is relatively rare in healthy humans from our analysis.

The dataset produced through this meta-analysis provides the most comprehensive overview, to date, of the normal HVR during acute hypoxia exposure, as well as the amplitude of the HVR following acclimatization to hypoxia. It also highlights the high level of variation in this reflex within and across individuals and populations. Our study was not designed to provide “normal values” for clinical settings such as those established for pulmonary function tests and arterial blood gas values. However, all of the data we used is available if it could be useful for such an effort. The data could also be used as a control group for experimental studies if comparable protocols are used. Our main conclusion, which should be applicable to other clinical or experimental studies, is that a low HVR is not necessarily “abnormal”. In earlier experimental studies, we might exclude a subject from further study if they had an extremely low (or negative) HVR measured during screening. Studies have shown that the HVR is reproducible within an individual (MacNutt et al 2015) so a low HVR measured during screening would likely be low in following sessions. However, our analysis suggests this exclusion of low HVRs is not appropriate and future work may show that a low HVR is even more common than this analysis suggests.

This meta-analysis also has some limitations. First, our analysis of the impact of hypoxia targets on mean HVR values depends on single lower-limit hypoxia targets reported in the methods of each study. However, experimental error will introduce variability in the actual hypoxia targets reached, and most studies do not indicate if HVR values were indeed calculated at these lower-limit points or if other criteria were used to choose data for HVR calculation. Similarly, particularly for rebreathing studies, it was not always stated if the HVR was calculated using a two-point calculation of change in ventilation per change in % SpO_2 (as is used for steady state methods), or if a linear regression across the entire range of SpO_2 levels was used. Nonetheless, with a substantial sample size, our data do not demonstrate significant impacts of SpO_2 targets on the amplitude of the HVR. Second, our data simulations do not account for individual variation and within-subject changes in hemoglobin-oxygen binding affinity, but instead depend on normal range values for estimates. However, these tests occur over short time periods (typically less than 30 minutes) and our simulations adjust for estimated changes in PCO_2 tensions at given PO_2 levels.

In conclusion, we demonstrate that lower HVRs are more common and higher HVRs are rare. This skewness of HVR measurements occurs across study methodologies. While isocapnic methods do produce higher HVR values, there is no impact of steady state or rebreathing methods on overall HVR when comparing across all studies. Finally, the experimental data examined here supports the predicted linear relationship between ventilation and SpO_2, at least at SpO_2 levels above about 75-80%, and while computational

investigations indicate that the level of hypoxia chosen may impact the amplitude of the HVR, this does not occur in vivo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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KEY POINTS

- The hypoxic ventilatory response (HVR) plays a crucial role in determining an individual's predisposition to hypoxia-related pathologies.
- There is notable variability in HVR sensitivity across individuals as well as significant population-level differences.
- We report that the normal distribution of the HVR is positively skewed, with a significant prevalence of low HVR values amongst the general healthy population. We also find no significant impact of the experimental protocol used to induce hypoxia, although HVR is greater with isocapnic versus poikilocapnic methods.
- These results provide insight into the normal distribution of the HVR, which could be useful in clinical decisions of diseases related to hypoxemia.
- Additionally, the low HVR values found within the general population provides insight into the genetic adaptations found in populations residing in high altitudes.

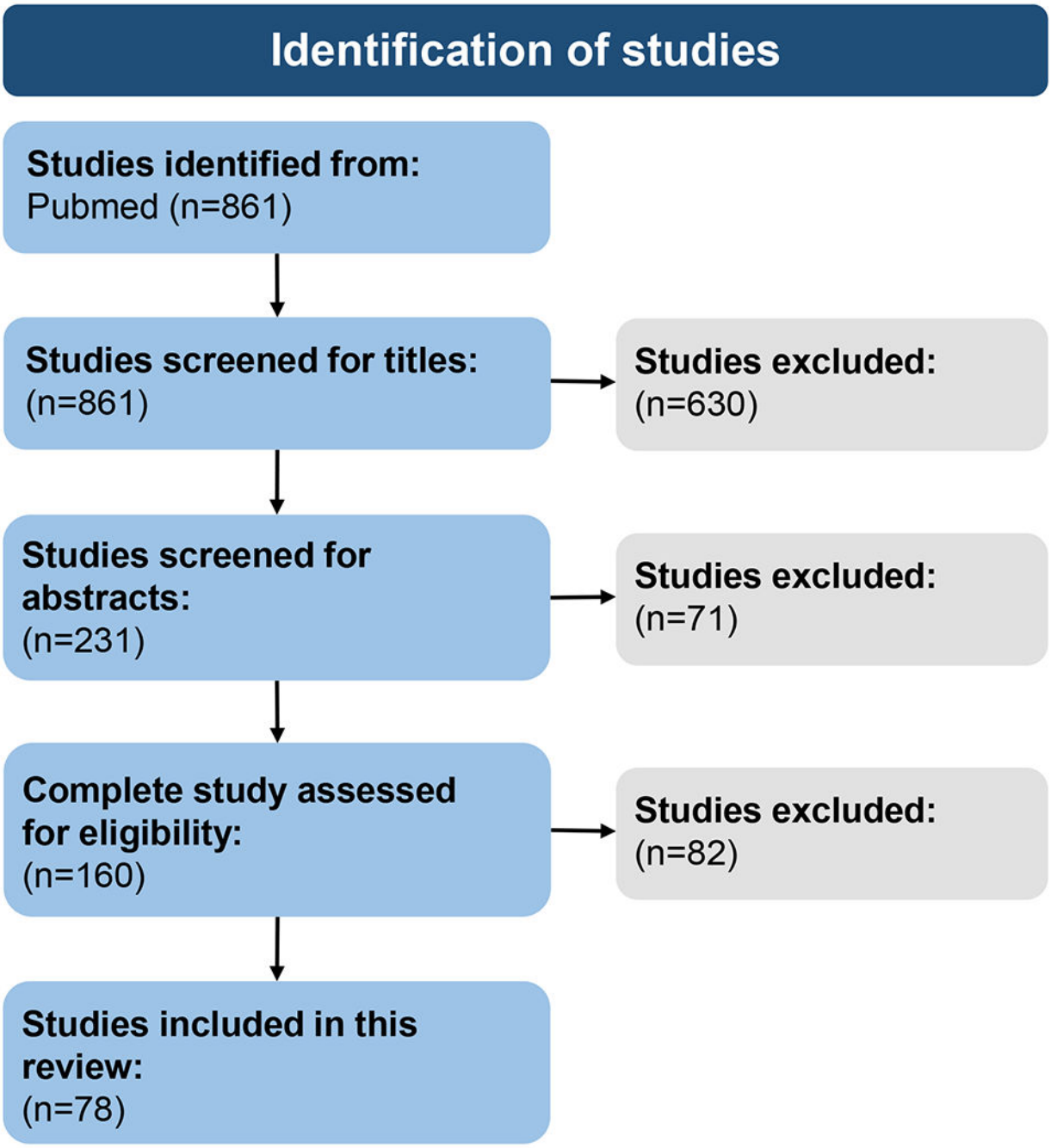

Figure 1. PRISMA diagram of study filtering.

Filtering methods and inclusion criteria used to identify studies for this analysis. A PubMed search conducted on August 12, 2021 using the terms “hypoxic ventilatory response” or “hypoxic chemosensitivity” across any time period yielded 861 reports. All reports were screened by title, and 630 reports were excluded due to the title indicating they were reviews, or providing no indication that any type or respiratory reflex was measured in humans. All remaining abstracts were then screened, and 71 of the remaining reports were excluded because of abstracts which did not indicate that HVR was measured in at least

one untreated healthy group. All remaining studies were then read in detail to verify that the study contained compatible study populations, compatible methodological approaches with sufficient detail provided, and compatible units ("L/min/SpO_2" or "A"), and that raw or mean HVR data was available for extraction. 82 reports were excluded during this step (Data not provided/incompatible data presentation (N=7), Insufficient methodological detail (N=5), Lack of healthy adult participants (N=3), Lack of non-intervention group (N=1), Incompatible methodology (N=34), Incompatible HVR unit (N=18), Inability to access report/not available in English language (N=14)). This yielded 78 compatible reports for analysis.

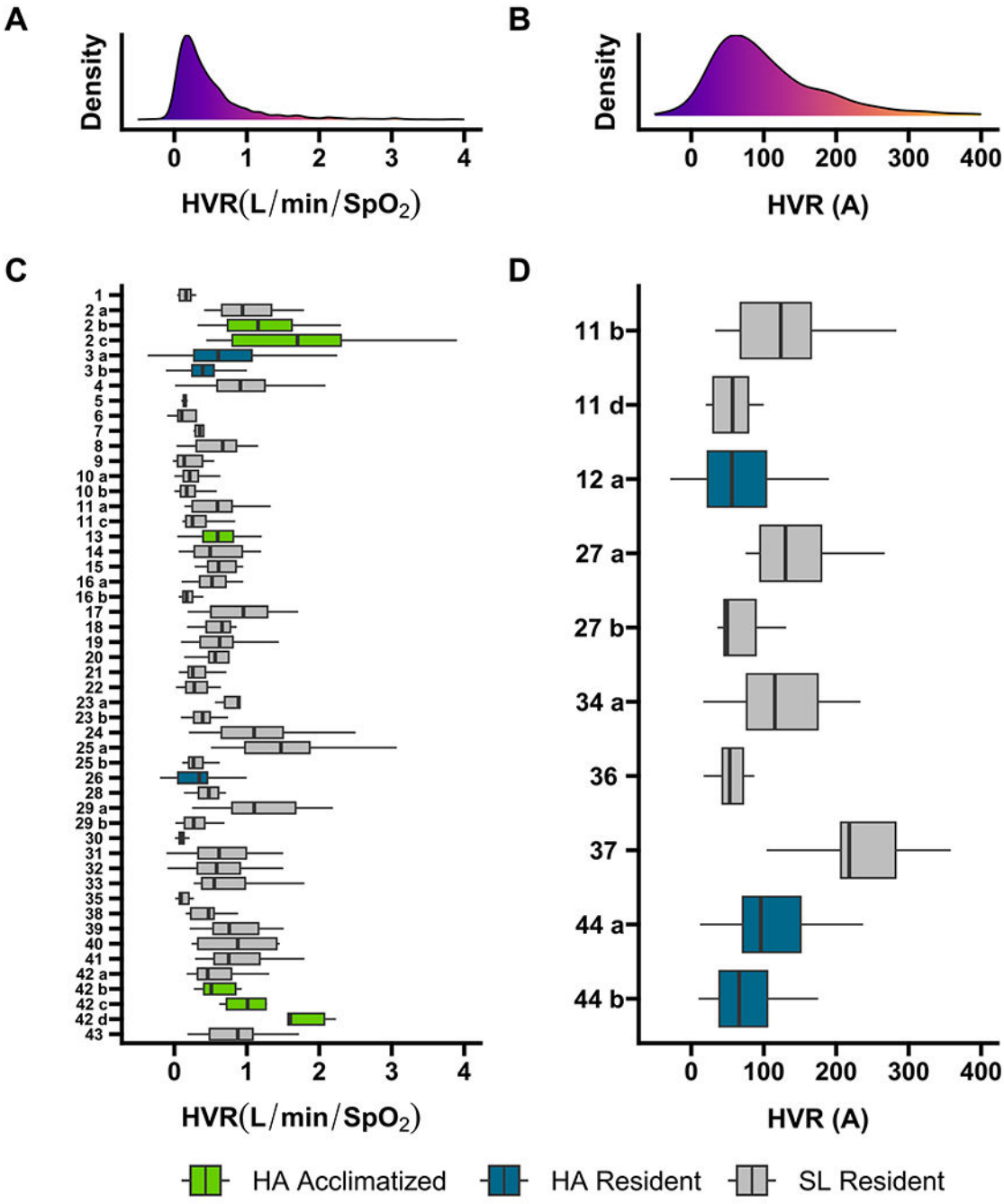

Figure 2. HVR distributions across studies.

(Top) Density plots showing pooled data across all studies, separated by HVR unit, "L/min/%SpO_2" **(A)** or "A" **(B)**. **(Bottom)** Boxplots showing distributions of HVR values within study datasets, separated by HVR unit, "L/min/%SpO_2" **(C)** or "A" **(D)**. For studies examining two distinct populations, data is separated into individual plots for each population within that study (i.e., 2a and 2b). Boxplot colors indicate the population examined in each dataset. Studies 3a, 12a, and 44a represent data collected in Tibetan or Sherpa high-altitude natives, and studies 3b and 26 represent data collected in Andean

high-altitude natives. Study 44b represents data collected in high-altitude residents of Han Chinese ancestry.

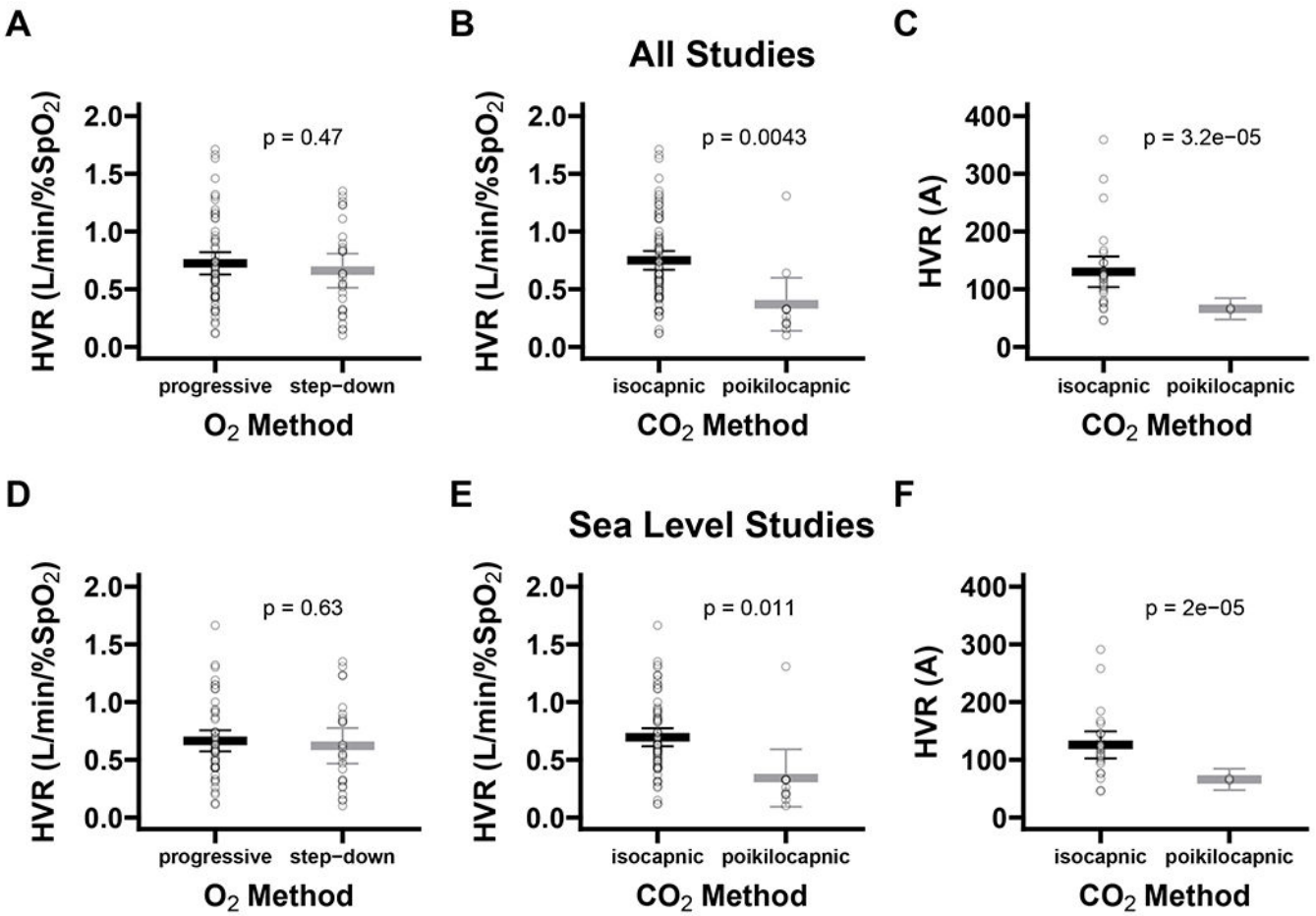

Figure 3. Impact of methodology on mean HVR.

Data points represent mean HVR values within an individual study. Data for all studies, including those in sea-level residents at sea level, high-altitude resident populations tested at high altitude, and sea-level residents acclimatized to high altitude are provided in panels **A-C**. Data for only studies conducted in sea-level residents at sea level are provided in panels **D-F**. Error bars represent 95% confidence intervals.

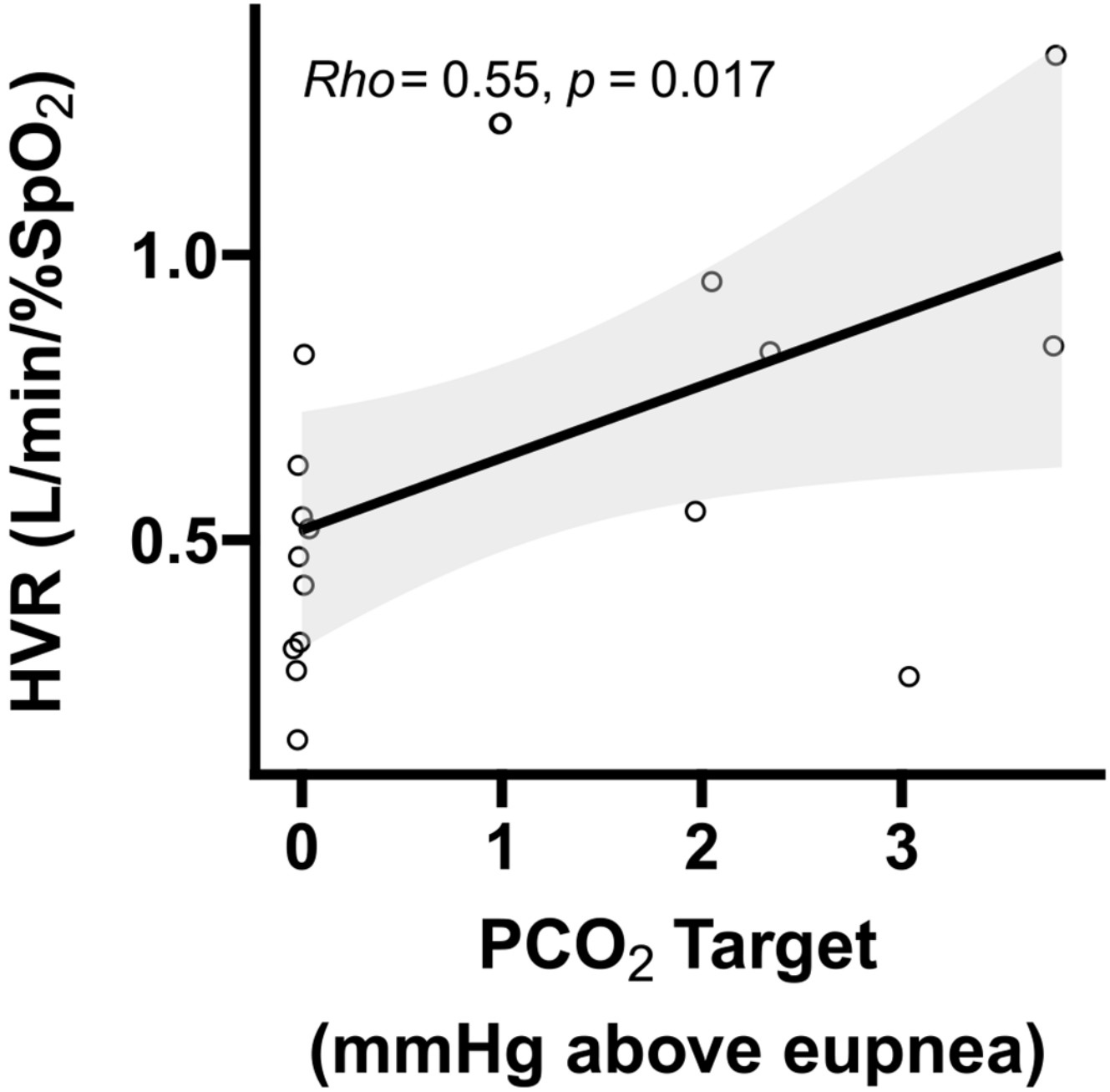

Figure 4. Spearman correlation plot for relationship between the HVR and end-tidal PCO_2 isocapnic target.

Data points represent mean HVR values for individual studies. Points are slightly jittered along the x axis for visibility of overlapping data. *Rho* and p values represent values calculated via a Spearman rank correlation analysis.

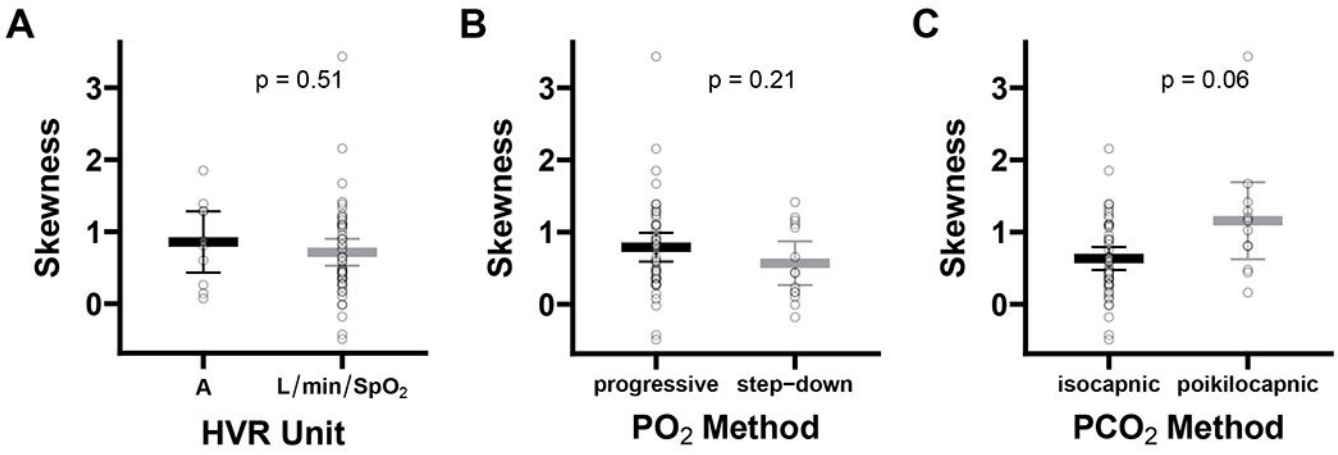

Figure 5. Impact of methodology on HVR distribution skewness.

Data points represent skewness of HVR value distributions within an individual study. Error bars represent 95% confidence intervals.

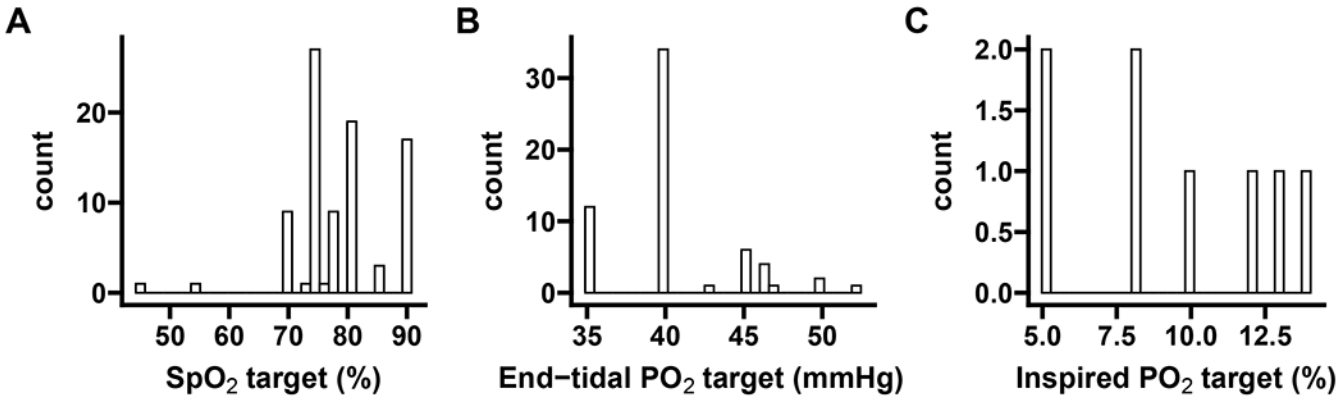

Figure 6. Histograms of experimental hypoxia targets chosen across all studies.

Hypoxia targets were determined for each individual study based on the target SpO_2 **(A)**, or end-tidal PO_2 target in mmHg **(B)** or % **(C)**. Results reported here include both hypoxia targets for step-down tests as well as low-end threshold hypoxia targets for progressive/ rebreathing methods.

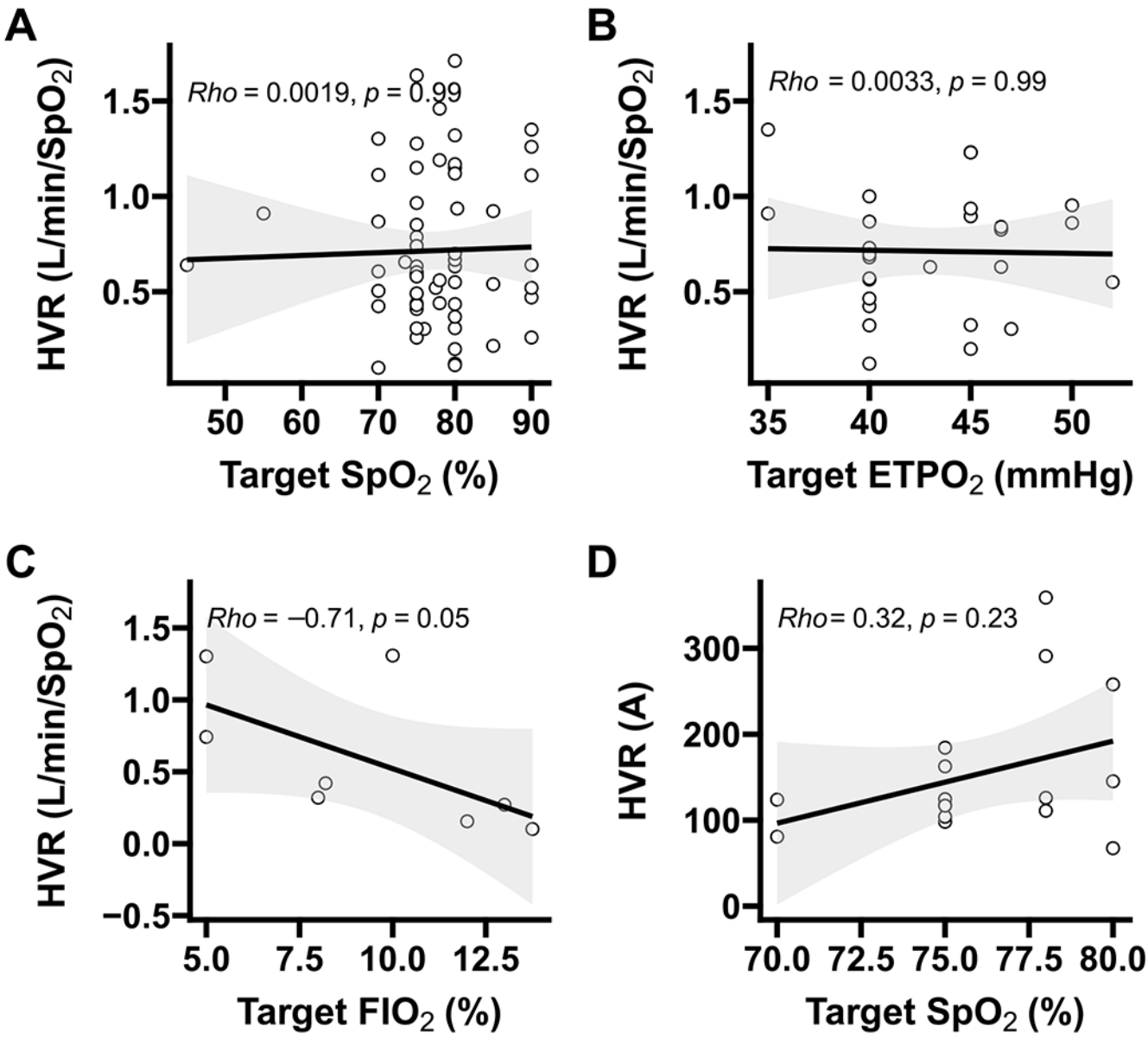

Figure 7. Mean HVR values as a function of target hypoxia level.

Relationships between mean HVR across studies and hypoxia targets for studies indicating SpO_2 (A), end-tidal PO_2 (B), and F_IO_2 targets (C) with L/min/SpO_2 units, as well as SpO_2 targets with A units (D).

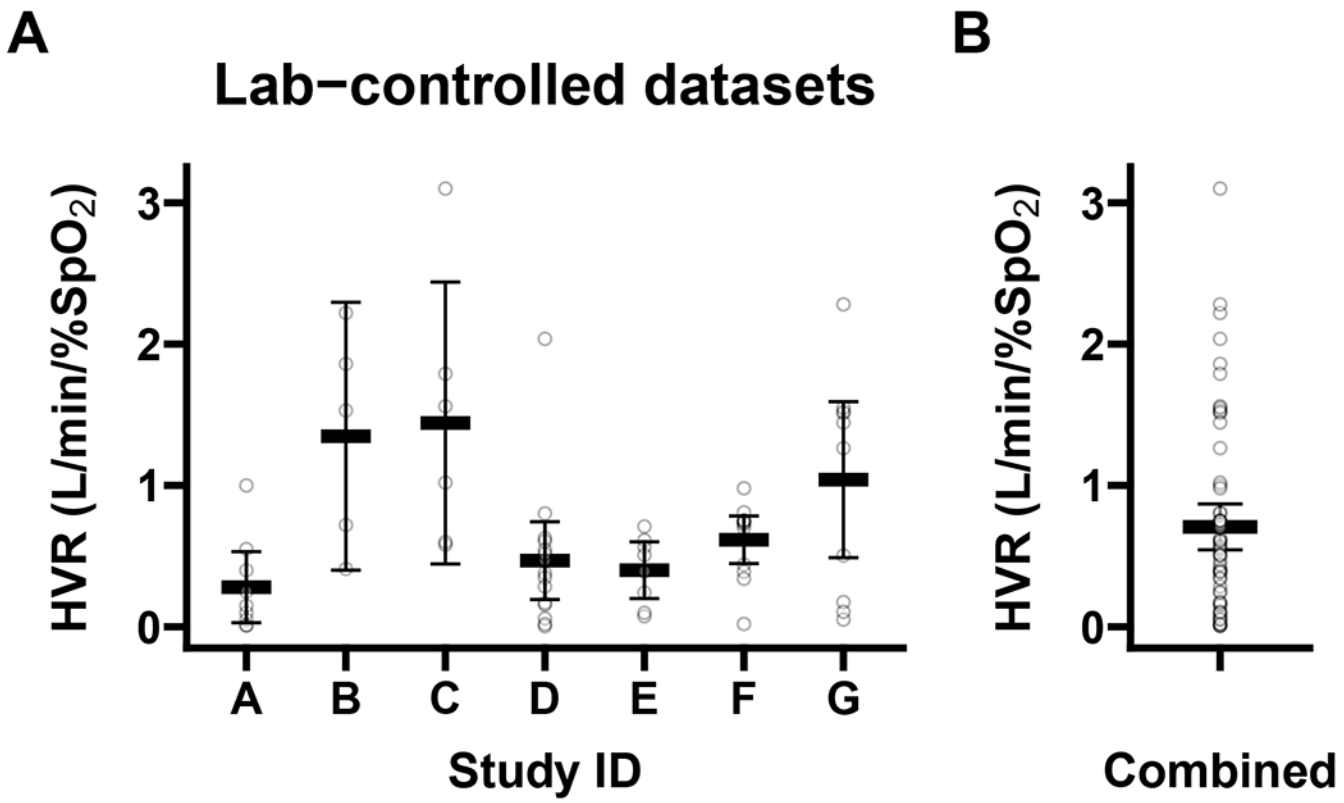

Figure 8. Distributions of lab-controlled datasets.

Datasets collected in the same laboratory all using isocapnic step-down protocols. Study IDs: A – Garcia et al. 2000, B – Hupperets et al. 2004, C – Weigner et al. 1998, D – Basaran et al. 1998, E – Unpublished 1, F – Unpublished 2, G – Unpublished 3.

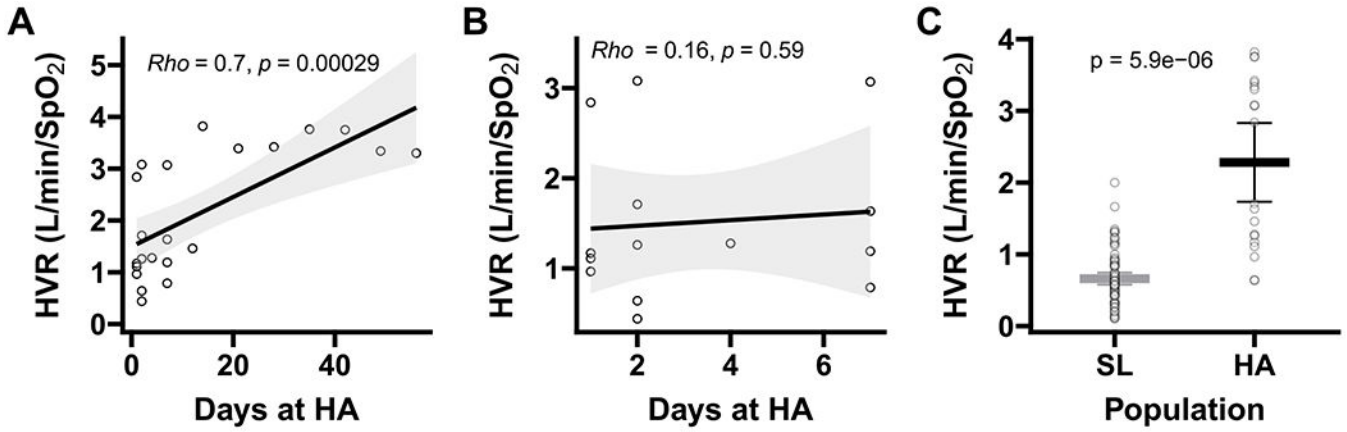

Figure 9. Impact of high-altitude acclimatization on the HVR.

(A) Mean HVR values collected from 19 datasets across 6 studies conducted at 3800 to 4559 m elevation. **(B)** An expanded view of mean HVR values from studies reporting 1-7 days of acclimatization at 3800 to 4559 m elevation. **(C)** Mean HVR values in all studies collecting HVR values in sea-level residents at sea level (SL) compared to sea-level residents acclimatized to 3800-4559 m elevation (HA).

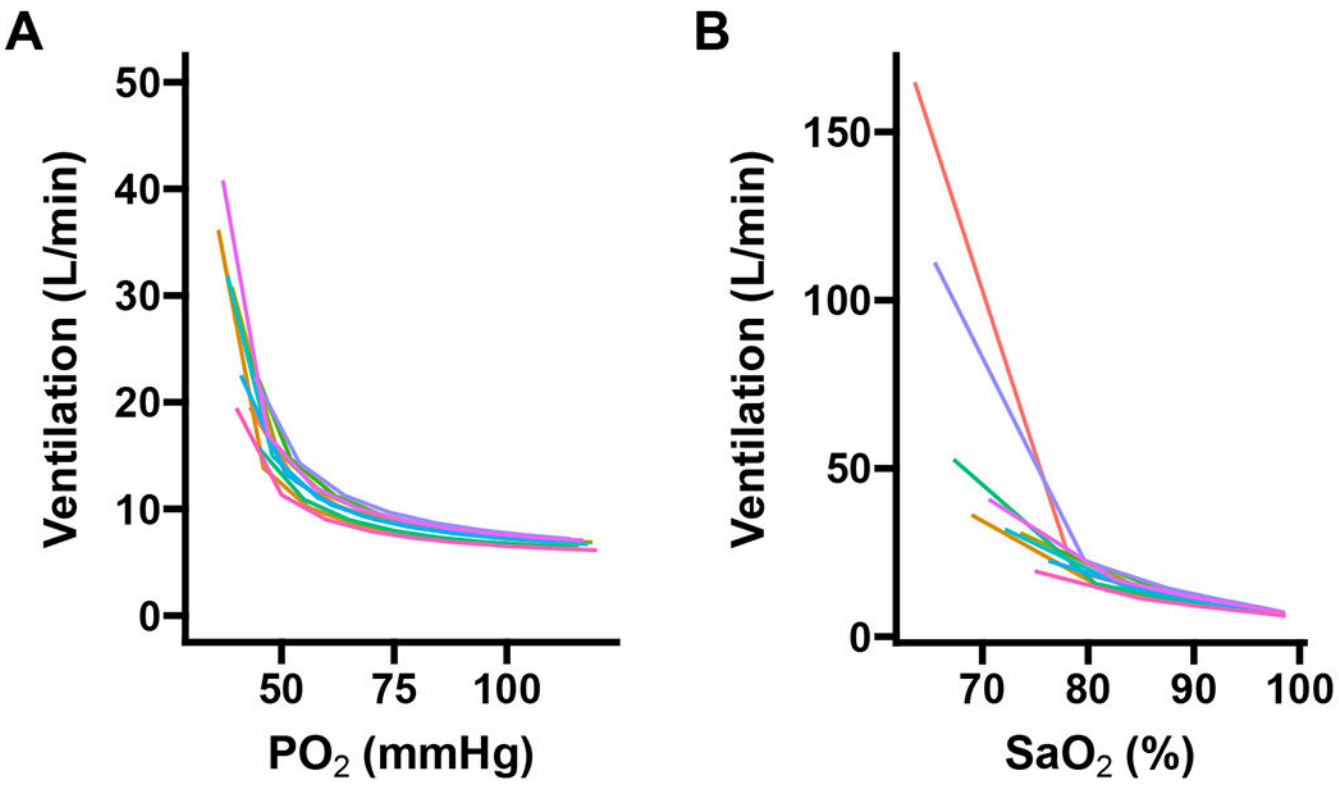

Figure 10. Simulated HVR curves.

A subset of 10 randomly generated HVR curves plotted as a function of PO_2 **(A)** or SaO_2 **(B)**. The same 10 datasets are plotted in A and B, and estimated SpO_2 levels in B were calculated from PO_2 in A as described above.

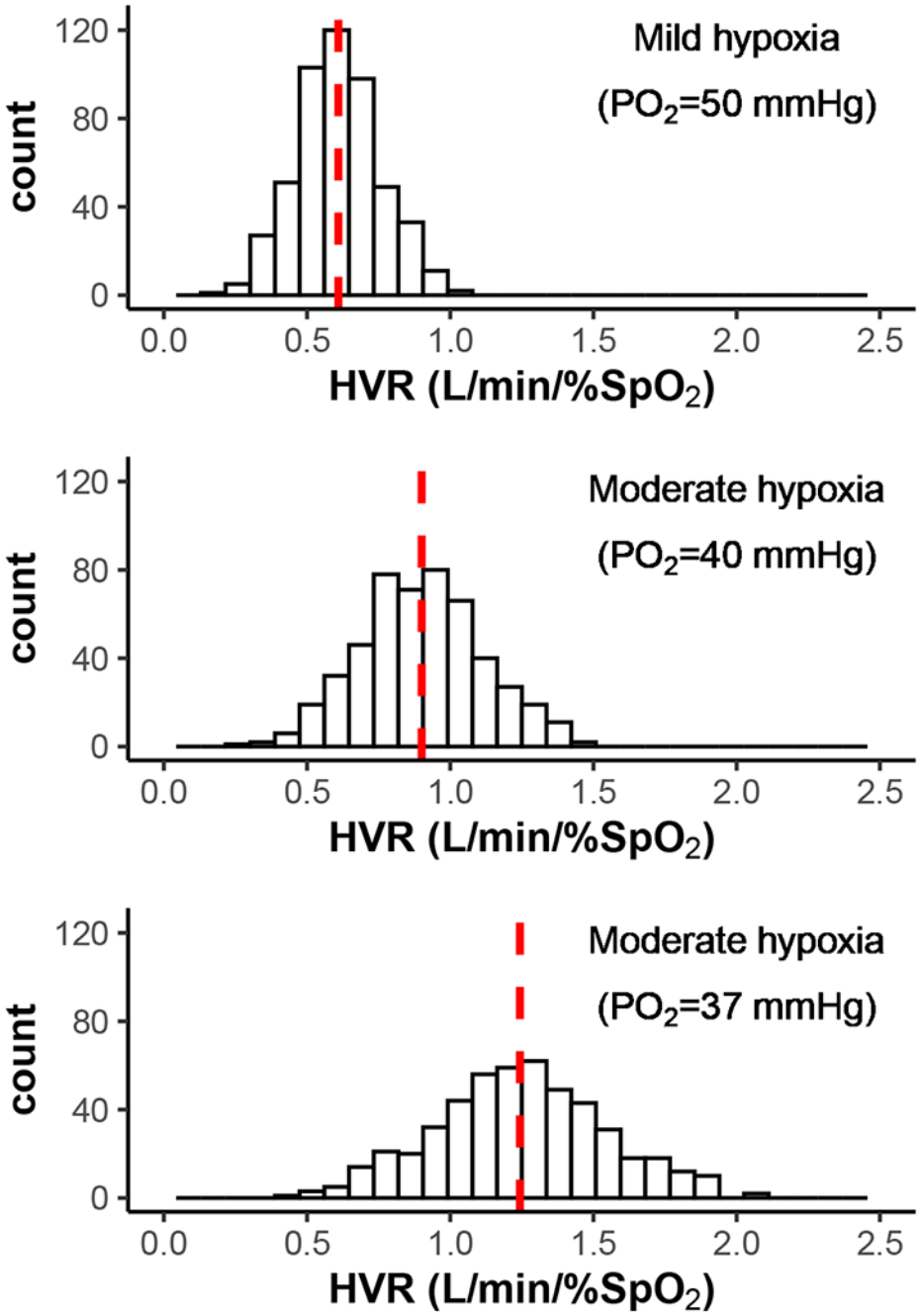

Figure 11. Distribution of simulated HVR values at different target PO_2 levels.

Plots display histogram distributions of 500 simulated HVR measurements with a target PO_2 at three levels across the same curves. The mean HVR in each group is indicated by vertical red dashed lines.